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 *          W E L C O M E   T O   T H E                        *
 *      U. S.  P A T E N T   T E X T   F I L E                  *
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=> s cd4(p)(ig or immunoglobulin or immunoglobin)(p)(fusion or chimeric or chimer)
        468 CD4
       3728 IG
       3434 IMMUNOGLOBULIN
        143 IMMUNOGLOBIN
      27348 FUSION
        534 CHIMERIC
          3 CHIMER
L1        6 CD4(P)(IG OR IMMUNOGLOBULIN OR IMMUNOGLOBIN)(P)(FUSION OR C
HIM
            ERIC OR CHIMER)

=> d ti ab kwic pd fd in ccls 1-6

US PAT NO:    5,234,905 [IMAGE AVAILABLE]          L1: 1 of 6
TITLE:        Soluble CD4 molecules modified to prolong circulating
              half-life

ABSTRACT:
A method for extending soluble CD4 serum half-life in mammals is
described. The method comprises modifying soluble CD4 glycosylation so as
to inhibit clearance from serum. In a preferred embodiment, clearance by
hepatocyte galactose receptors is inhibited by removal of soluble CD4
terminal sialic residues followed by oxidation of exposed galactose
residues. The modified soluble CD4 molecules are demonstrated to possess
extended serum half-life.

SUMMARY:

BSUM(8)

 The use of soluble forms of **CD4** has been proposed for AIDS treatment
or prophylaxis (See e.g., EP 0 385,909, published Sep. 5, 1990). Soluble
forms of **CD4** are known to have a short half-life in circulation in
relation to certain serum proteins. Because the in vivo plasma half-life
of soluble **CD4** has been shown to be relatively short, various
strategies have been employed to stabilize the protein against clearance.
(See, e.g.,. . . 90/01035; and WO 90/05534). Conjugates have been
prepared in which polyethylene glycol or other hydrophilic polymers are
attached to the **CD4** either via amino acid free functional groups or
via sugar moieties in the oligosaccharide side chains of the glycosylated
soluble **CD4** protein. A second approach to stabilizing the **CD4**
protein in circulation has been to produce **fusion** proteins including
a soluble **CD4** portion and a portion from a protein of long
circulating half-life, such as an **immunoglobulin**. Such fusions
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exhibited longer plasma half-lives in animal models than sCD4 without added domains.
DATE ISSUED: Aug. 10, 1993
DATE FILED: Feb. 22, 1991
INVENTOR: J. Fred Kolhouse, Denver, CO
John C. Deutsch, Denver, CO
US-CL-CURRENT: 514/8; 530/350, 395, 402

US PAT NO: 5,231,167 [IMAGE AVAILABLE] L1: 2 of 6
TITLE: Immunoglobulin-binding polypeptides

ABSTRACT:
Polypeptides having a segment capable of binding to immunoglobulin heavy chain variable regions (V.sub.H) in an antigen independent manner have been described. These polypeptides can be used to form complexes with V.sub.M containing molecules for diagnostic purposes and to increase the affinity of the antibody for its antigen. Additionally, the polypeptides of the invention can be used to separate V.sub.H containing molecules from solution to form isolated V.sub.H or V.sub.H depleted compositions.

DETDESC:

DETD(13)

In . . . polypeptide of the present invention has an amino acid residue sequence corresponding to a portion of the sequence of the **CD4** molecule, exhibits antigen-independent affinity for the V.sub.H region of **Ig** molecules, and is substantially, free from the ability to bind the human immunodeficiency virus. Methods for determining the ability of a **CD4**-related polypeptide to bind HIV are well known in the art and typically involve examining the ability of a polypeptide to inhibit HIV-induced cell **fusion** (syncytium formation). See, for example, Jameson, et al., Science. 240:1335-1338 (1988). (The references cited herein are hereby incorporated by reference.)

DETDESC:

DETD(31)

Preferably, . . . and more preferably at least about 25, amino acid residues having a sequence that is heterologous to the sequence of **CD4**. A heterologous **CD4** amino acid residue sequence is a sequence that does not immunologically cross-react with **CD4**. In preferred embodiments, the second segment of a subject **chimeric** polypeptide is comprised of a sequence of amino acid residues capable of binding the F.sub.C portion of an **Ig** molecule, i.e., is an F.sub.C -binding segment.

DETDESC:

DETD(36)

The antigen-independent **Ig**-binding segments (i.e., the V.sub.H -binding and F.sub.C -binding segments) of a subject **chimeric**

polypeptide can be either contiguous or adjacent to each other within the polypeptide chain. Where they are adjacent, the segments. . . 50 residues, preferably about 15 to about 30 residues as are found in Protein A and Protein G. A subject **chimeric** polypeptide can contain a plurality of the same or different V.sub.H -binding and F.sub.C -binding segments. Where three or more of the **Ig**-binding segments are adjacent within a subject **chimeric** polypeptide, the spacer segments can be the same or different. It is preferred that the amino acid residue sequence of. . . Protein G. A spacer segment can also be comprised of a sequence of residue corresponding to a portion of the **CD4** sequence that is contiguous to one of the V.sub.H -binding regions of **CD4** as described herein.

DATE ISSUED: Jul. 27, 1993
DATE FILED: Sep. 8, 1989
INVENTOR: Maurizio Zanetti, La Jolla, CA
Petar Lenert, San Diego, CA
Edward Golub, La Jolla, CA
Daniel Kroon, Bridgewater, NJ
US-CL-CURRENT: 530/324, 300, 326, 350, 412, 413

US PAT NO: 5,225,538 [IMAGE AVAILABLE] L1: 3 of 6
TITLE: Lymphocyte homing receptor/immunoglobulin fusion proteins

ABSTRACT:
Novel polypeptides are provided, together with methods for making and using them, and nucleic acids encoding them. These polypeptides are useful as cell surface adhesion molecules and ligands, and are useful in therapeutic or diagnostic compositions and methods.

SUMMARY:

BSUM(29)

A particular multichain **fusion** of this sort is one in which the variable region of one **immunoglobulin** chain has been substituted by the ligand binding region of a first receptor such as **CD4** while the variable region of another **immunoglobulin** chain has been substituted by a binding functionality of the LHR, both **immunoglobulin** chains being associated with one another in substantially normal fashion.

DETDESC:

DETD(3)

As used herein, the term "ligand binding partner" specifically excludes polymorphic and nonpolymorphic members of the **immunoglobulin** gene superfamily, and proteins which are homologous thereto, such as class I and class II major histocompatibility antigens, immunoglobulins, T-cell receptor .alpha., .beta., .gamma. and .delta. chains, CD1, CD2, **CD4**, CD8, CD28, the .gamma., .delta. and .epsilon. chains of CD3, OX-2, Thy-1, the intercellular or neural cell adhesion molecules (I-CAM or N-CAM), lymphocyte function associated antigen-3 (LFA-3), neurocytoplasmic protein (NCP-3), poly-**Ig** receptor, myelin-associated glycoprotein (MAG), high affinity IgE receptor, the major glycoprotein of peripheral

myelin (Po), platelet derived growth factor receptor, colony stimulating factor-1 receptor, macrophage Fc receptor, Fc gamma receptors and carcinoembryonic antigen. Homologous to a member of the **immunoglobulin** gene superfamily, for the purposes of this exclusion only, means having the sequence of a member of the **immunoglobulin** gene superfamily or having a sequence therewithin which has substantially the same (or a greater degree of) amino acid sequence. . . homology to a known member of the superfamily as the specific examples given above have to the sequence of an **immunoglobulin** variable or constant domain. Note that this does not exclude embodiments in which a ligand binding partner **fusion** is assembled into a multimer with, in addition, a member or **fusion** of a member of the **immunoglobulin** gene superfamily.

DATE ISSUED: Jul. 6, 1993
DATE FILED: Dec. 16, 1991
INVENTOR: Daniel J. Capon, San Mateo, CA
Laurence A. Lasky, Sausalito, CA
US-CL-CURRENT: 530/387.3; 435/69.7; 530/388.73

US PAT NO: 5,206,353 [IMAGE AVAILABLE] L1: 4 of 6
TITLE: CD-4/cytotoxic gene fusions

ABSTRACT:
A chimeric gene directing the synthesis of hybrid recombinant fusion protein in a suitable expression vector has been constructed. The fusion protein possesses the property of selective cytotoxicity against specific virus-infected cells. A CD4(178)-PE40 hybrid fusion protein has been made for selectively killing HIV-infected cells.

DETDESC:

DETD(12)

A 0.70-kb EcoRI-SalI fragment containing the amino-terminal two **immunoglobulin**-like domains of **CD4** was excised from pCD4f and cloned into M13mp18. The resulting recombinat phage, mp18CD4TM1 was propagated in a dut.sup.- ung.sup.- strain. . . site (CATATG) encoding histidine and methionine residues just after a codon encoding an alanine residue, the 178th amino acid of **CD4**. After second strand synthesis, the double-stranded DNA was transformed into a wild type strain, and a mutant clone mp18CD4TM21 was selected by NdeI digestion. To obtain a final expression plasmid for a **fusion** protein more easily, an intermediate plasmid, pCD4PE40TM1 was constructed as follows. A 1.23-kb fragment containing PE40 was excised from pVC8. . . digesting it with XbaI. The fragment was ligated with a 5.21-kb fragment of pCD4TM1 (an expression plasmid for 372 amino-acid **CD4**); the fragment was obtained by digesting the plasmid with SalI, filling in the cohesive end with DNA polymerase I Klenow. . . and ligated with a 0.69-kb NdeI-EcoRI fragment of mp18CD4TM21, yielding pCD4SPE40TM1. This plasmid is capable of expressing a 546 amino-acid **fusion** protein consisting of the first 178 amino acids of **CD4** at the amino terminus, followed by histidine and methionine residues derived from the NdeI site used for joining the two. . .

DETDESC:

DETD(39)
II. . . . composed of an anti-gp120 mouse monoclonal antibody chemically conjugated to protein toxin (ricin) has also been reported. However, the CD4(178)-PE40 **fusion** protein of the present invention possesses numerous advantages over this immunotoxin: (a) In the case of the immunotoxin the antibody. . . contrast, CD4(178)-PE40 may be used against divergent strains of HIV-1 as well as against HIV-2, since all these viruses use **CD4** as the receptor. Because of this requirement for **CD4** receptor specificity, it is extremely unlikely that variants of HIV, resistant to **CD4**-toxin hybrid proteins, will arise, whereas variants which no longer bind type-specific monoclonal antibodies often arise. (b) The immunotoxin is produced. . . to control, thereby compromising the uniformity of the conjugate and also result in low yield. In contrast, the recombinant CD4(178)-PE40 **fusion** protein can be produced in large quantities in a bacterial expression system using standard procedures. (c) The mouse **immunoglobulin** component of the immunotoxin is likely to be immunogenic in human subjects, thereby compromising its effectiveness. In contrast, with **CD4**-toxin **fusion** proteins, the targeting to gp120-expressing cells is achieved by a fragment of human **CD4**, which is likely to be less immunogenic in humans.
DATE ISSUED: Apr. 27, 1993
DATE FILED: Jul. 22, 1988
INVENTOR: Edward A. Berger, Rockville, MD
Bernard Moss, Bethesda, MD
Thomas R. Fuerst, Gaithersburg, MD
Ira Pastan, Potomac, MD
David Fitzgerald, Silver Spring, MD
Tamio Mizukami, Bethesda, MD
Vijay K. Chaudhary, Rockville, MD
US-CL-CURRENT: 536/23.4; 435/69.7, 172.3, 252.33, 320.1

US PAT NO: 5,116,964 [IMAGE AVAILABLE] L1: 5 of 6
TITLE: Hybrid immunoglobulins

ABSTRACT:
Immunoglobulin fusion polypeptides are provided, together with methods for making and using them, and nucleic acids encoding them. These polypeptides are useful as cell surface adhesion molecules and ligands, and are useful in therapeutic or diagnostic compositions and methods.

SUMMARY:

BSUM(30)

A particular multichain **fusion** of this sort is one in which the variable region of one **immunoglobulin** chain has been substituted by the ligand binding region of a first receptor such as **CD4** while the variable region of another **immunoglobulin** chain has been substituted by a binding functionality of the LHR, both **immunoglobulin** chains being associated with one another in substantially normal fashion.

DETDESC:

DETD(3)

As used herein, the term "ligand binding partner" specifically excludes polymorphic and nonpolymorphic members of the **immunoglobulin** gene superfamily, and proteins which are homologous thereto, such as class I and class II major histocompatibility antigens, immunoglobulins, T-cell receptor .alpha., .beta., .gamma. and .delta. chains, CD1, CD2, **CD4**, CD8, CD28, the .gamma., .delta. and .epsilon. chains of CD3, OX-2, Thy-1, the intercellular or neural cell adhesion molecules (I-CAM or N-CAM), lymphocyte function associated antigen.3 (LFA.3), neurocytoplasmic protein (NCP-3) poly-**Ig** receptor myelin-associated glycoprotein (MAG), high affinity IgE receptor, the major glycoprotein of peripheral myelin (Po), platelet derived growth factor receptor, colony stimulating factor.1 receptor, macrophage Fc receptor, Fc gamma receptors and carcinoembryonic antigen. Homologous to a member of the **immunoglobulin** gene superfamily, for the purposes of this exclusion only, means having the sequence of a member of the **immunoglobulin** gene superfamily or having a sequence therewithin which has substantially the same (or a greater degree of) amino acid sequence. . . homology to a known member of the superfamily as the specific examples given above have to the sequence of an **immunoglobulin** variable or constant domain. Note that this does not exclude embodiments in which a ligand binding partner **fusion** is assembled into a multimer with, in addition, a member or **fusion** of a member of the **immunoglobulin** gene superfamily.

DATE ISSUED: May 26, 1992
DATE FILED: Nov. 22, 1989
INVENTOR: Daniel J. Capon, San Mateo, CA
Laurence A. Lasky, Sausalito, CA
US-CL-CURRENT: 536/23.5; 435/69.7, 252.3, 320.1; 530/350; 536/23.51, 23.53

US PAT NO: 5,109,123 [IMAGE AVAILABLE] L1: 6 of 6
TITLE: Alteration of ability of soluble CD4 fragments to bind HIV

ABSTRACT:
DNA encoding modified soluble human CD4 fragments whose ability to bind to the HIV gp120 envelope protein is different from the ability of soluble human CD4 fragments; modified soluble human CD4 fragments having altered gp120 binding ability, methods of making such fragments and methods of using such fragments.

SUMMARY:

BSUM(3)

Human **CD4** is also the receptor for the gp120 envelope glycoprotein of the human immunodeficiency virus (HIV) and is essential for virus entry into the host cell, and for membrane **fusion**, which both contribute to cell-to-cell transmission of the virus and to its cytopathic effects. Klatzmann, D., et al., Science, 225:. . . (1986); Sodroski, J., et al., Nature, 322: 470-474 (1986); Lifson, J., et al.,

Nature, 323: 725-728 (1986). Sequence analysis of **CD4** has suggested an evolutionary origin from a structure with four **immunoglobulin**-related domains. Clark, S., et al. Proc. Natl. Acad. Sci., 84: 1649-1653 (1987); Littman, D. R., et al., Nature, 325: 453-455. . .
DATE ISSUED: Apr. 28, 1992
DATE FILED: Jul. 11, 1988
INVENTOR: Ellis L. Reinherz, Lincoln, MA
Linda K. Clayton, Jamaica Plain, MA
US-CL-CURRENT: 536/23.72; 435/91.41, 91.5, 91.53, 172.3, 235.1; 935/1, 9, 10, 11, 12, 65

=> s cd4
L2 468 CD4

=> s l2 and recombinant not l1
4837 RECOMBINANT
L3 155 L2 AND RECOMBINANT NOT L1

=> s l3 and (cd4/ti or cd4/ab)
6 CD4/TI
18 CD4/AB
L4 8 L3 AND (CD4/TI OR CD4/AB)

=> d 1-8

1. 5,225,535, Jul. 6, 1993, Lymphokine SAF and method of making; Elaine C. DeFreitas, et al., 530/351; 424/85.1 [IMAGE AVAILABLE]

2. 5,185,250, Feb. 9, 1993, Human .gamma., .delta.T cell antigen receptor polypeptides and nucleic acids; Michael B. Brenner, et al., 435/69.3, 7.24, 69.1, 172.2, 240.27; 530/350, 387.9, 388.22, 388.75; 536/23.5 [IMAGE AVAILABLE]

3. 5,171,838, Dec. 15, 1992, Leu3a binding peptides; Yukinobu Chiba, 530/326, 324 [IMAGE AVAILABLE]

4. 5,155,037, Oct. 13, 1992, Insect signal sequences useful to improve the efficiency of processing and secretion of foreign genes in insect systems; Max D. Summers, 435/240.2, 172.3, 240.1, 240.21, 320.1; 536/23.7, 24.1; 935/32, 48, 70 [IMAGE AVAILABLE]

5. 5,149,785, Sep. 22, 1992, Proteins which regulate gene expression of the interleukin-2 receptor and of human lymphotropic retroviruses; Harvey I. Cantor, et al., 530/350, 397; 930/25; 935/36 [IMAGE AVAILABLE]

6. 5,126,433, Jun. 30, 1992, Soluble forms of the T cell surface protein **CD4**; Paul J. Maddon, et al., 530/395, 350, 380, 387.2, 387.9, 389.1 [IMAGE AVAILABLE]

7. 5,023,328, Jun. 11, 1991, Lepidopteran AKH signal sequence; Max D. Summers, et al., 536/23.5; 435/69.4; 536/23.1 [IMAGE AVAILABLE]

8. 4,952,499, Aug. 28, 1990, Genes and their encoded proteins which regulate gene expression of the interleukin-2 receptor and of human

lymphotropic retroviruses; Harvey I. Cantor, et al., 435/69.1, 172.1, 172.3, 240.2, 252.33, 320.1; 536/23.52, 23.72, 24.1 [IMAGE AVAILABLE]

=> d ab 6

US PAT NO: 5,126,433 [IMAGE AVAILABLE] L4: 6 of 8

ABSTRACT:
A single-stranded nucleic acid molecule which encodes an amino acid sequence comprising at least a portion of a T4 glycoprotein is provided. Additionally, amino acid sequences which comprise at least a portion of a T4 glycoprotein and are useful as a prophylaxis for treating a subject with acquired immune deficiency syndrome are provided. These amino acid sequences, are capable of specifically forming a complex with a human immunodeficiency virus envelope glycoprotein and which are soluble in an aqueous solution. Monoclonal antibodies directed to the water-soluble amino acid sequences of the present invention may be used as vaccines for immunizing a subject against acquired immune deficiency syndrome.

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Antibodies--Administration and Dosage--AD; HIV Infections--Therapy--TH; HIV-1--Immunology--IM; Immunotherapy; Neutralization Tests; T virus-free cell *fusion* assay was developed, using Chinese hamster ovary cells that stably express HIV-1 gp120/gp41. These cells were incubated with dilutions of *CD4* -based molecules, antibodies, or mixtures of both, then overlaid with C8166 *CD4*+ T cells. Syncytia were counted and the degree of inhibition of cell *fusion* was determined. Synergy, additivity, or antagonism was calculated by the combination index (CI) method. The *CD4*-based molecules included soluble human *CD4* as well as *fusion* proteins composed of *CD4* linked to human *immunoglobulin* gamma 1 or gamma 2 heavy chains. Combinations of *CD4*-based molecules and monoclonal or polyclonal anti-V3 loop antibodies were synergistic in blocking HIV-1 envelope-mediated cell *fusion* (CI = 0.21-0.91 at 95% inhibition). Synergy was also observed with combinations of the *CD4* -based molecules and a broadly neutralizing anti-gp41 monoclonal antibody (2F5) (CI = 0.29

8/3,AB,KWIC/1 (Item 1 from file: 157)
00090916 93378778 MED/93378778

Synergistic inhibition of HIV-1 envelope-mediated cell *fusion* by *CD4* -based molecules in combination with antibodies to gp120 or gp41.

Allaway GP; Ryder AM; Beaudry GA; *Maddon PJ*
Progenics Pharmaceuticals, Inc., Tarrytown, New York 10591.

AIDS Res Hum Retroviruses Jul 1993, 9 (7) p581-7, ISSN 0889-2229
Journal Code: ART
Contract/Grant No.: NIAID 1 R43 AI32813-01, A1, NIAID
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

CD4 -based molecules were tested in combination with HIV-1-neutralizing antibodies directed against the V3 loop of gp120 or against gp41, for inhibition of HIV-1 envelope-mediated cell *fusion*. A virus-free cell *fusion* assay was developed, using Chinese hamster ovary cells that stably express HIV-1 gp120/gp41. These cells were incubated with dilutions of *CD4* -based molecules, antibodies, or mixtures of both, then overlaid with C8166 *CD4*+ T cells. Syncytia were counted and the degree of inhibition of cell *fusion* was determined. Synergy, additivity, or antagonism was calculated by the combination index (CI) method. The *CD4*-based molecules included soluble human *CD4* as well as *fusion* proteins composed of *CD4* linked to human *immunoglobulin* gamma 1 or gamma 2 heavy chains. Combinations of *CD4*-based molecules and monoclonal or polyclonal anti-V3 loop antibodies were synergistic in blocking HIV-1 envelope-mediated cell *fusion* (CI = 0.21-0.91 at 95% inhibition). Synergy was also observed with combinations of the *CD4* -based molecules and a broadly neutralizing anti-gp41 monoclonal antibody (2F5) (CI = 0.29-0.65 at 95% inhibition). These results demonstrate that molecules inhibiting HIV attachment act synergistically with molecules inhibiting HIV-1 *fusion* . The results suggest that *CD4*-based therapeutics would be more effective in patients with naturally occurring anti-V3 loop or anti-gp41 antibodies. In addition, there may be an advantage in coadministering *CD4*-based molecules and antibodies that block *fusion*, especially broadly neutralizing anti-gp41 antibodies, as a combination therapy for HIV-1 infections.

Synergistic inhibition of HIV-1 envelope-mediated cell *fusion* by *CD4* -based molecules in combination with antibodies to gp120 or gp41.

Allaway GP; Ryder AM; Beaudry GA; *Maddon PJ*

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CD4 -based molecules, antibodies, or mixtures of both, then overlaid with C8166 *CD4*+ T cells. Syncytia were counted and the degree of inhibition of cell *fusion* was determined. Synergy, additivity, or antagonism was calculated by the combination index (CI) method. The *CD4*-based molecules included soluble human *CD4* as well as *fusion* proteins composed of *CD4* linked to human *immunoglobulin* gamma 1 or gamma 2 heavy chains. Combinations of *CD4*-based molecules and monoclonal or polyclonal anti-V3 loop antibodies were synergistic in blocking HIV-1 envelope-mediated cell *fusion* (CI = 0.21-0.91 at 95% inhibition). Synergy was also observed with combinations of the *CD4* -based molecules and a broadly neutralizing anti-gp41 monoclonal antibody (2F5) (CI = 0.29-0.65 at 95% inhibition). These results demonstrate that molecules inhibiting HIV attachment act synergistically with molecules inhibiting HIV-1 *fusion* . The results suggest that *CD4*-based therapeutics would be more effective in patients with naturally occurring anti-V3 loop or anti-gp41 antibodies. In addition, there may be an advantage in coadministering *CD4*-based molecules and antibodies that block *fusion*, especially broadly neutralizing anti-gp41 antibodies, as a combination therapy for HIV-1 infections.

Descriptors: Antigens, *CD4*--Pharmacology--PD; **CD4* Immunoadhesins --Pharmacology--PD; *Gene Products, env--Immunology--IM; *Giant Cells; *HIV Antibodies--Immunology--IM; *HIV-1--Pathogenicity--PY; Amino Acid Sequence; Cell *Fusion*; CHO Cells; Drug Synergism; Hamsters; Hela Cells; HIV Envelope Protein gp120--Immunology--IM; HIV Envelope Protein gp41 --Immunology--IM; HIV-1--Immunology--IM; Molecular Sequence Data; Neutralization Tests; Peptide Fragments--Immunology--IM; Recombinant *Fusion* Proteins--Pharmacology--PD; Recombinant Proteins--Pharmacology--PD

Chemical Name: Antigens, *CD4*; (*CD4* Immunoadhesins; (Gene Products, env; (HIV envelope protein gp120 (305-321); (HIV Antibodies; (HIV Envelope Protein gp120; (HIV Envelope Protein gp41; (Peptide Fragments; (Recombinant *Fusion* Proteins; (Recombinant Proteins; (SK&F 106528

8/3,AB,KWIC/2 (Item 2 from file: 157)

00085032 93333438 ICA9/93333438

A virus-free assay of HIV-1-induced cell *fusion* for analysis of synergy between *CD4*-based molecules and antibodies to the V3 loop of gp120 or to gp41.

Allaway GP; Ryder AM; Beaudry GA; *Maddon PJ*

Progenics Pharmaceuticals Inc., Tarrytown, New York.

Int Conf AIDS Jun 6-11 1993, 9 (1) p137 (abstract no. PO-A01-0017),

Contract/Grant No.: 1 R43 AI32813-01, AI, NIAID

Languages: ENGLISH

Document Type: MEETING ABSTRACT

CD4 -based molecules were tested in combination with neutralizing antibodies to gp120 or gp41 for inhibition of HIV-1 envelope-mediated cell *fusion*. A virus-free cell *fusion* assay was developed using Chinese Hamster Ovary cells which stably express HIV-1LAI gp120/gp41. These cells were incubated with dilutions of *CD4*-based molecules, antibodies, or mixtures of both, then overlayed with C8166 *CD4*+ T cells. Syncytia were counted and the degree of inhibition of cell *fusion* determined. Synergy, additivity or antagonism was calculated by the Combination Index (CI) method. The *CD4*-based molecules included soluble *CD4* and dimeric *CD4*-*immunoglobulin* *chimeras* . These molecules were synergistic in combination with a monoclonal anti-V3 loop antibody (CI = 0.21-0.71 at 95% inhibition), and mildly synergistic in combination with a polyclonal anti-V3 loop serum (CI = 0.81-0.91 at 95% inhibition). Combinations of *CD4* -based molecules and a broadly neutralizing anti-gp41 antibody were also synergistic (CI = 0.29-0.65 at 95% inhibition). These results add weight to the idea that molecules which block HIV attachment, such as *CD4* -based molecules, act synergistically with molecules which block HIV-1 *fusion* , including antibodies to the V3 loop or to gp41. This suggests that *CD4* -based therapeutics would be more effective in patients who exhibit naturally occurring anti-V3 loop or anti-gp41 antibodies. There may be an advantage in co-administering *CD4*-based molecules with antibodies which block HIV-1 *fusion* as a combination therapy for HIV-1 infections.

A virus-free assay of HIV-1-induced cell *fusion* for analysis of synergy

2

A virus-free assay of HIV-1-induced cell *fusion* for analysis of synergy between *CD4*-based molecules and antibodies to the V3 loop of gp120 or to gp41.

Allaway GP; Ryder AM; Beaudry GA; *Maddon PJ*

CD4 -based molecules were tested in combination with neutralizing antibodies to gp120 or gp41 for inhibition of HIV-1 envelope-mediated cell *fusion*. A virus-free cell *fusion* assay was developed using Chinese Hamster Ovary cells which stably express HIV-1LAI gp120/gp41. These cells were incubated with dilutions of *CD4*-based molecules, antibodies, or mixtures of both, then overlayed with C8166 *CD4*+ T cells. Syncytia were counted and the degree of inhibition of cell *fusion* determined. Synergy, additivity or antagonism was calculated by the Combination Index (CI) method. The *CD4*-based molecules included soluble *CD4* and dimeric *CD4*-*immunoglobulin* *chimeras* . These molecules were synergistic in combination with a monoclonal anti-V3 loop antibody (CI = 0.21-0.71 at 95% inhibition), and mildly synergistic in combination with a polyclonal anti-V3 loop serum (CI = 0.81-0.91 at 95% inhibition). Combinations of *CD4* -based molecules and a broadly neutralizing anti-gp41 antibody were also synergistic (CI = 0.29-0.65 at 95% inhibition). These results add weight to the idea that molecules which block HIV attachment, such as *CD4* -based molecules, act synergistically with molecules which block HIV-1 *fusion* , including antibodies to the V3 loop or to gp41. This suggests that *CD4* -based therapeutics would be more effective in patients who exhibit naturally occurring anti-V3 loop or anti-gp41 antibodies. There may be an advantage in co-administering *CD4*-based molecules with antibodies which block HIV-1 *fusion* as a combination therapy for HIV-1 infections.

Descriptors: Antigens, *CD4*--Physiology--PH; *HIV Envelope Protein gp120 --Physiology--PH; *HIV Envelope Protein gp41--Physiology--PH; *HIV-1 --Physiology--PH; *Peptide Fragments--Physiology--PH; Binding, Competitive; Cell *Fusion*--Physiology--PH; CHO Cells--Microbiology--MI; Hamsters; HIV Antibodies--Administration and Dosage--AD; HIV Infections--Therapy--TH; HIV-1--Immunology--IM; Immunotherapy; Neutralization Tests; T4...

Chemical Name: Antigens, *CD4*; (HIV envelope protein gp120 (305-321); (HIV Antibodies; (HIV Envelope Protein gp120; (HIV Envelope Protein gp41 ; (Peptide Fragments

?ds

Set	Items	Description
S1	142	CD4 AND (IG OR IMMUNOGLOBIN OR IMMUNOGLOBULIN) AND (FUSION OR CHIMER?)
S2	101	RD (unique items)
S3	2	AU="BEAUDRY G"
S4	45	E3-E5
S5	47	S3 OR S4
S6	30	RD (unique items)
S7	2	S6 AND S1
S8	2	S6 AND S2

?s s2 not s8

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            101  S2
              2  S8
     S9      99  S2 NOT S8
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?s s9 and py<1992

Processing

Processing

Processing

?

12/3/1 (Item 1 from file: 157)

00075923 10029790 ICA6/10029790

T cell functions and phenotypes in SCID-hu mice.

Krowka J; Sarin S; Namikawa R; McCune JM; Kaneshima H

SyStemix, Inc., Palo Alto, CA, USA

Int Conf AIDS Jun 20-23 1990, 6 (1) p194 (abstract no. Th.A.297),

Languages: ENGLISH

Document Type: MEETING ABSTRACT

3

12/3/2 (Item 2 from file: 157)
[illegible]

[illegible] antibody [illegible] for AIDS therapy.

[illegible]; Loetscher E; Steiner [illegible] Jack HM; Wabl [illegible]

Department of Microbiology and Immunology and Laboratory of Radiobiology and Environmental Health, University of California, San Francisco, California, USA

Int Conf AIDS Jun 20-23 1990, 6 (1) p178 (abstract no. Th.A.234),

Languages: ENGLISH

Document Type: MEETING ABSTRACT

BEST AVAILABLE COPY

12/3/3 (Item 3 from file: 157)
00071055 0330292 ASM91/0330292

Expression of *CD4* and HIV-specific immunoglobulins in bacteria.

McCallus DE; Ugen KE; Williams WV; Weiner DB

The Wistar Insitute and the University of Pennsylvania, Philadelphia, PA.

Abstr Annu Meet Am Soc Microbiol May 5-9 1991, 91 p337 (abstract no. T-20), ISSN 0094-8519

Languages: ENGLISH

Document Type: MEETING ABSTRACT

12/3/4 (Item 4 from file: 157)
00070971 40112190 ICA6/40112190

CD4-*immunoglobulin* *fusion* proteins with effector function on HIV and HIV-infected cells.

Zettlmeissl G; Gregersen JP; Langner KD; Niedrig M; Gelderblom H; Seed B

Research Laboratories of Behringwerke AG, Marburg, FRG

Int Conf AIDS Jun 20-23 1990, 6 (2) p344 (abstract no. 1121),

Languages: ENGLISH

Document Type: MEETING ABSTRACT

12/3/5 (Item 5 from file: 157)
00068736 4002991 ICA7/4002991

Analysis of mutations in the HIV-1 envelope glycoprotein that affect *fusion* and infectivity.

Page KA; Stearns SM; Littman DR

Dept. of Microbiology, University of California, San Francisco, CA, USA

Int Conf AIDS Jun 16-21 1991, 7 (2) p63 (abstract no. TH.A.29),

Languages: ENGLISH

Document Type: MEETING ABSTRACT

12/3/6 (Item 6 from file: 157)
00066739 00355689 ICA5/00355689

A *CD4*-*immunoglobulin* *fusion* protein as a candidate for AIDS therapy.

Zettlmeissl GW; Gregersen JP; Duport JM; Seed B

Research Laboratories of Behringwerke AG, Marburg, FRG

Int Conf AIDS Jun 4-9 1989, 5 p674 (abstract no. C.697),

ISBN 0-662-56670-X

Languages: ENGLISH

Document Type: MEETING ABSTRACT

12/3/7 (Item 7 from file: 157)
00061447 00335289 ICA5/00335289

Quantifying HIV infectivity.

Layne SP; Spouge JL; Dembo M

Los Alamos National Laboratory, University of California, Los Alamos, NM, USA

Int Conf AIDS Jun 4-9 1989, 5 p633 (abstract no. Th.C.P.100),

ISBN 0-662-56670-X

Languages: ENGLISH

Document Type: MEETING ABSTRACT

12/3/8 (Item 8 from file: 157)

Basel Institute for Immunology), Basel, Switzerland
Int Conf AIDS Jun 4-9 1989, 5 p582 (abstract no. T.C.P.96),
ISBN 0-662-56670-X
Languages: ENGLISH
Document Type: MEETING ABSTRACT

12/3/9 (Item 9 from file: 157)
00061258 00289489 ICA5/00289489
Expression and characterization of *chimeric* proteins containing human *CD4* linked to human *immunoglobulin* heavy chain constant regions.
Mizukami T; Smith CD; Berger EA; Moss B
Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA
Int Conf AIDS Jun 4-9 1989, 5 p556 (abstract no. M.C.P.89),
ISBN 0-662-56670-X
Languages: ENGLISH
Document Type: MEETING ABSTRACT

12/3/10 (Item 10 from file: 157)
00056440 89650737 ICDB/89650737
STRUCTURAL BASIS OF *CD4* BINDING TO GP120 AND THE DEVELOPMENT OF SOLUBLE *CD4* ANALOGS AS ANTI HIV-1 THERAPEUTICS (MEETING ABSTRACT)
Smith D; Marsters S; Ashkenazi A; Peralta E; Byrn R; Groopman J; Gregory T; Capon DJ
Dept. of Molecular Biology, Genentech, Inc., S. San Francisco, CA
Fourth International Conference on AIDS. Book II. June 12-16, 1988, Stockholm, Sweden, p. 56, 1988.
Languages: ENGLISH
Document Type: MEETING ABSTRACT

12/3/11 (Item 11 from file: 157)
00044517 92149490 MED/92149490
Evaluation of anti-human immunodeficiency virus effect of recombinant *CD4*-*immunoglobulin* in vitro: a good candidate for AIDS treatment.
Chowdhury IH; Koyanagi Y; Takamatsu K; Yoshida O; Kobayashi S; Yamamoto N
Department of Microbiology, Tokyo Medical and Dental University School of Medicine, Japan.
Med Microbiol Immunol (Berl) 1991, 180 (4) p183-92, ISSN 0300-8584 Journal Code: M58
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/12 (Item 12 from file: 157)
00042093 92046304 MED/92046304
Broadly neutralizing antibodies targeted to mucin-type carbohydrate epitopes of human immunodeficiency virus.
Hansen JE; Nielsen C; Arendrup M; Olofsson S; Mathiesen L; Nielsen JO; Clausen H
Department of Infectious Diseases 144, Hvidovre Hospital, Denmark.
J Virol Dec 1991, 65 (12) p6461-7, ISSN 0022-538X Journal Code: KCV
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/13 (Item 13 from file: 157)
00041713 92030380 MED/92030380
Construction of *CD4*-based *chimeric* molecules by chemical cross-linking.
Idziorek T; Klatzmann D
Laboratoire de Biologie et Genetique des Infections Retrovirales, Mat. CERVI, Hopital de la Pitie, Paris, France.
AIDS Res Hum Retroviruses Jun 1991, 7 (6) p529-36, ISSN 0889-2229 Journal Code: ART
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

5

12/3/14 (Item 14 from file: 157)
00040458 91104898 MED/91104898
Enzymatic cleavage of a *CD4* immunoadhesin generates crystallizable, biologically active Fd-like fragments.
Chamow SM; Peers DH; Byrn RA; Mulkerrin MJ; Harris KJ; Wang WC; Bjorkman PJ; Capon DJ; Ashkenazi A
Department of Recovery Process Research and Development, Genentech, Inc., South San Francisco, California 94080.
Biochemistry Oct 23 1990, 29 (42) p9885-91, ISSN 0006-2960 Journal Code: A0G
Contract/Grant No.: AI-28931, AI, NIAID; HL-43510, HL, NHLBI; HL-42374, HL, NHLBI; +
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/15 (Item 15 from file: 157)
00039953 90226048 MED/90226048
A CD 4: *immunoglobulin* *fusion* protein with antiviral effects against HIV.
Gregersen JP; Mehdi S; Gelderblom H; Zettlmeissl G
Research Laboratories, Behringwerke AG, Marburg, Federal Republic of Germany.
Arch Virol 1990, 111 (1-2) p29-43, ISSN 0304-8608 Journal Code: 8L7
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/16 (Item 16 from file: 157)
00039870 90182664 MED/90182664
A *CD4* domain important for HIV-mediated syncytium formation lies outside the virus binding site.
Camerini D; Seed B
Department of Genetics, Harvard Medical School, Boston, Massachusetts.
Cell Mar 9 1990, 60 (5) p747-54, ISSN 0092-8674 Journal Code: CQ4
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/17 (Item 17 from file: 157)
00038820 91333020 MED/91333020
Recombinant *CD4*-selected human immunodeficiency virus type 1 variants with reduced gp120 affinity for *CD4* and increased cell *fusion* capacity.
McKeating J; Balfe P; Clapham P; Weiss RA
Chester Beatty Laboratories, Institute of Cancer Research, London, United Kingdom.
J Virol Sep 1991, 65 (9) p4777-85, ISSN 0022-538X Journal Code: KCV
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/18 (Item 18 from file: 157)
00038173 91302370 MED/91302370
Stilbene disulfonic acids. *CD4* antagonists that block human immunodeficiency virus type-1 growth at multiple stages of the virus life cycle.
Cardin AD; Smith PL; Hyde L; Blankenship DT; Bowlin TL; Schroeder K; Stauderman KA; Taylor DL; Tyms AS
Marion Merrell Dow Research Institute, Cincinnati, Ohio 45215.
J Biol Chem Jul 15 1991, 266 (20) p13355-63, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/19 (Item 19 from file: 157)
00038126 91299366 MED/91299366
CD4 -Pseudomonas exotoxin hybrid proteins: modulation of potency and therapeutic window through structural design and characterization of cell internalization.

Kosa M; Griffiths BA; Wall M; et al
BIOGEN, Inc., Cambridge, MA.
AIDS Res Hum Retroviruses Apr 1991, 7 (4) p393-401, ISSN 0889-2229
Journal Code: ART
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/20 (Item 20 from file: 157)
00035460 91174332 MED/91174332
Peptides derived from the CDR3-homologous domain of the *CD4* molecule are specific inhibitors of HIV-1 and SIV infection, virus-induced cell *fusion* , and postinfection viral transmission in vitro. Implications for the design of small peptide anti-HIV therapeutic agents.
Rausch DM; Hwang KM; Padgett M; Voltz AH; Rivas A; Engleman E; Gaston I; McGrath M; Fraser B; Kalyanaraman VS; et al
Laboratory of Cell Biology, National Institute of Mental Health, Bethesda, Maryland 20892.
Ann N Y Acad Sci 1990, 616 p125-48, ISSN 0077-8923 Journal Code: 5NM
Contract/Grant No.: CA 24607, CA, NCI; AI 25922, AI, NIAID
Languages: ENGLISH
Document Type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

12/3/21 (Item 21 from file: 157)
00035348 91170280 MED/91170280
A region in domain 1 of *CD4* distinct from the primary gp120 binding site is involved in HIV infection and virus-mediated *fusion*.
Truneh A; Buck D; Cassatt DR; Juszczak R; Kassis S; Kyu SE; Healey D; Sweet R; Sattentau Q
Department of Cell Sciences, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania 19406.
J Biol Chem Mar 25 1991, 266 (9) p5942-8, ISSN 0021-9258
Journal Code: HIV
Contract/Grant No.: AI 26462, AI, NIAID
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/22 (Item 22 from file: 157)
00034613 91131153 MED/91131153
The iscom: an immunostimulating system.
Morein B
Department of Virology, National Veterinary Institute, Uppsala, Sweden.
Immunol Lett Aug 1990, 25 (1-3) p281-3, ISSN 0165-2478
Journal Code: GIH
Languages: ENGLISH
Document Type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

12/3/23 (Item 23 from file: 157)
00034328 91118016 MED/91118016
Human immunodeficiency virus infection of human-PBL-SCID mice.
Mosier DE; Gulizia RJ; Baird SM; Wilson DB; Spector DH; Spector SA
Division of Immunology, Medical Biology Institute, La Jolla, CA 92037.
Science Feb 15 1991, 251 (4995) p791-4, ISSN 0036-8075
Journal Code: UJ7
Contract/Grant No.: AI-27763, AI, NIAID; AI-29182, AI, NIAID
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/24 (Item 24 from file: 157)
00033751 91085548 MED/91085548
CD4 -affinity purification of recombinant and native HIV gp120 and comparison of the affinity constants for the receptor.
Moritz D; Dirckx L; Mous J; Schneider J
Central Research Units, F. Hoffman-La Roche Ltd., Basel, Switzerland.

Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/25 (Item 25 from file: 157)
00033548 91075655 MED/91075655
[Human immunodeficiency virus infect[illegible]d the pathogenesis of AIDS]
Infekce virem lidskeho imunodeficitu a patogeneze onemocneni AIDS.
Krejsek J; Fixa B
II. katedra internich obor.ANG.u, farmakologie a lekarske biochemie LF UK v Hradci Kralove.
Vnitr Lek Oct 1990, 36 (10) p1025-9, ISSN 0042-773X Journal Code: XFY
Languages: CZECH Summary Languages: ENGLISH
Document Type: JOURNAL ARTICLE English Abstract

12/3/26 (Item 26 from file: 157)
00033256 91061882 MED/91061882
Crystal structure of an HIV-binding recombinant fragment of human *CD4* [see comments]
Ryu SE; Kwong PD; Truneh A; Porter TG; Arthos J; Rosenberg M; Dai XP; Xuong NH; Axel R; Sweet RW; et al
Department of Biochemistry and Molecular Biophysics, Columbia University, New York, New York 10032.
Nature Nov 29 1990, 348 (6300) p419-26, ISSN 0028-0836 Journal Code: NSC
Comment in Nature 1990 Nov 29;348(6300):393-4
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/27 (Item 27 from file: 157)
00031682 90321469 MED/90321469
Expression and characterization of human *CD4*:*immunoglobulin* *fusion* proteins.
Zettlmeissl G; Gregersen JP; Duport JM; Mehdi S; Reiner G; Seed B
Research Laboratories of Behringwerke AG, Marburg, West Germany.
DNA Cell Biol Jun 1990, 9 (5) p347-53, ISSN 1044-5498 Journal Code: AF9
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/28 (Item 28 from file: 157)
00030745 90376482 MED/90376482
CD4 immunoadhesin, but not recombinant soluble *CD4*, blocks syncytium formation by human immunodeficiency virus type 2-infected lymphoid cells.
Sekigawa I; Chamow SM; Groopman JE; Byrn RA
Department of Medicine, New England Deaconess Hospital, Harvrd Medical School, Boston, Massachusetts 02215.
J Virol Oct 1990, 64 (10) p5194-8, ISSN 0022-538X Journal Code: KCV
Contract/Grant No.: HL33774, HL, NHLBI; HL42112, HL, NHLBI; HL43510, HL, NHLBI; +
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/29 (Item 29 from file: 157)
00027020 88235916 MED/88235916
Location and chemical synthesis of a binding site for HIV-1 on the *CD4* protein.
Jameson BA; Rao PE; Kong LI; Hahn BH; Shaw GM; Hood LE; Kent SB
Division of Biology, California Institute of Technology, Pasadena 91125.
Science Jun 3 1988, 240 (4857) p1335-9, ISSN 0036-8075 Journal Code: UJ7
Contract/Grant No.: AI25784
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

00026032 90078997 MED/90078997
A *chimeric* mouse-human antibody that retains specificity for HIV gp120 and mediates the lysis of HIV-infected cells.
Liou RS; Rosen EM; Fung MS; Sun WN; Sun C; Gordon W; Chang NT; Chang TW
Tanox Biosystems, Inc., Houston, TX 77025.
J Immunol Dec 15 1989, 143 (12) p3967-75, ISSN 0022-1767
Journal Code: IFB
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/31 (Item 31 from file: 157)
00025007 90212782 MED/90212782
Lessons from past experience in cancer immunotherapy and their application to cancer and AIDS treatment and prophylaxis.
Mathe G
Institut du Cancer et d'Immunogenetique, Immunitaires et Tumorales, Hopital Paul-Brousse, Villejuif, France.
Biomed Pharmacother 1989, 43 (8) p551-61, ISSN 0753-3322
Journal Code: A59
Languages: ENGLISH
Document Type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

12/3/32 (Item 32 from file: 157)
00022437 90063052 MED/90063052
Characterization of the surface topography and putative tertiary structure of the human CD7 molecule.
Ware RE; Scearce RM; Dietz MA; Starmer CF; Parker TJ; Haynes BF
Department of Medicine, Duke University Medical Center, Durham, NC 27710.
J Immunol Dec 1 1989, 143 (11) p3632-40, ISSN 0022-1767
Journal Code: IFB
Contract/Grant No.: CA28936; K11-HL02015
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/33 (Item 33 from file: 157)
00021510 89249309 MED/89249309
Identification of the residues in human *CD4* critical for the binding of HIV.
Arthos J; Deen KC; Chaikin MA; Fornwald JA; Sathe G; Sattentau QJ; Clapham PR; Weiss RA; McDougal JS; Pietropaolo C; et al
Smith Kline and French Laboratories, King of Prussia, Pennsylvania 19406.
Cell May 5 1989, 57 (3) p469-81, ISSN 0092-8674 Journal Code: CQ4
Languages: ENGLISH
Document Type: JOURNAL ARTICLE

12/3/34 (Item 1 from file: 155)
07924808 92062808
Autoimmune syndrome after neonatal induction of tolerance to alloantigens: analysis of the specificity and of the cellular and genetic origin of autoantibodies.
Schurmans S; Merino J; Qin HY; Kramar G; Duchosal M; Skalli O; Benzonana G; Gabbiani G; Lambert PH
WHO Immunology Research and Training Center, Geneva, Switzerland.
Autoimmunity 1991, 9 (4) p283-91, ISSN 0891-6934 Journal Code: A5H
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/35 (Item 2 from file: 155)
07901088 92039088
Chimerization of antibodies by isolation of rearranged genomic variable regions by the polymerase chain reaction.
Weissenhorn W; Weiss E; Schwirzke M; Kaluza B; Weidle UH
Institut fur Immunologie, Universitat Munchen, F.R.G.
Gene Oct 15 1991 106 (2) p273-7 ISSN 0378-1119 Journal Code: GNE

Document type: JOURNAL ARTICLE

12/3/36 (Item 3 from file: 155)
07800693 91319693
Vascular cell adhesion molecule 1 induces T-cell antigen receptor-dependent activation of *CD4*+ T lymphocytes.
Damle NK; Aruffo A
Oncogen Division, Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA 98121.
Proc Natl Acad Sci U S A Aug 1 1991, 88 (15) p6403-7, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/37 (Item 4 from file: 155)
07720531 91239531
Reshaping a therapeutic *CD4* antibody.
Gorman SD; Clark MR; Routledge EG; Cobbold SP; Waldmann H
Department of Pathology, University of Cambridge, United Kingdom.
Proc Natl Acad Sci U S A May 15 1991, 88 (10) p4181-5, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/38 (Item 5 from file: 155)
07686303 91205303
Engraftment and development of human T and B cells in mice after bone marrow transplantation.
Lubin I; Faktorowich Y; Lapidot T; Gan Y; Eshhar Z; Gazit E; Levite M; Reisner Y
Department of Biophysics, Weizmann Institute of Science, Rehovot, Israel.
Science Apr 19 1991, 252 (5004) p427-31, ISSN 0036-8075 Journal Code: UJ7
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/39 (Item 6 from file: 155)
07565586 91084586
Observations on the effect of *chimeric* anti-*CD4* monoclonal antibody in patients with mycosis fungoides.
Knox SJ; Levy R; Hodgkinson S; Bell R; Brown S; Wood GS; Hoppe R; Abel EA ; Steinman L; Berger RG; et al
Department of Radiation Oncology, Stanford University School of Medicine, CA 94305.
Blood Jan 1 1991, 77 (1) p20-30, ISSN 0006-4971 Journal Code: A8G
Contract/Grant No.: CA34233, CA, NCI; M01-RR00070, RR, NCRR
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/40 (Item 7 from file: 155)
07440179 90347179
A T cell receptor V alpha region selectively expressed in *CD4*+ cells.
Jameson SC; Kaye J; Gascoigne NR
Department of Immunology, Research Institute of Scripps Clinic, La Jolla, CA 92037.
J Immunol Sep 1 1990, 145 (5) p1324-31, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: GM-39476, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/41 (Item 8 from file: 155)
07184092 90091092
Functional human T cell-B cell hybridomas established from *fusion* of normal T cells and [illegible]

Journal Code: DEA
Contract/Grant No.: CA-12800, CA, NCI; AI-15251, AI, NIAID; AI-15332, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/42 (Item 9 from file: 155)
07050889 89352889
Peripheral lymph node helper T-cell recovery after syngeneic bone marrow transplantation in mice prepared with either gamma-irradiation or busulfan.
Samlowski WE; Araneo BA; Butler MO; Fung MC; Johnson HM
Salt Lake City VA Medical Center, UT 84132.
Blood Sep 1989, 74 (4) p1436-45, ISSN 0006-4971 Journal Code: A8G
Contract/Grant No.: CA 45354
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/43 (Item 10 from file: 155)
06933180 89235180
The expression and sequences of T cell antigen receptor beta-chain genes in the thymus at an early stage after sublethal irradiation.
Yuuki H; Yoshikai Y; Kishihara K; Matsuzaki G; Ayukawa K; Nomoto K
Department of Immunology, Kyushu University, Fukuoka, Japan.
J Immunol May 15 1989, 142 (10) p3683-91, ISSN 0022-1767
Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/44 (Item 11 from file: 155)
06901262 89203262
Influence of the major histocompatibility complex on positive thymic selection of V beta 17a+ T cells.
Blackman MA; Marrack P; Kappler J
Howard Hughes Medical Institute, Denver, CO.
Science Apr 14 1989, 244 (4901) p214-7, ISSN 0036-8075
Journal Code: UJ7
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/45 (Item 12 from file: 155)
06874864 89176864
Induction of classical transplantation tolerance in the adult.
Qin SX; Cobbold S; Benjamin R; Waldmann H
Department of Pathology, University of Cambridge, United Kingdom.
J Exp Med Mar 1 1989, 169 (3) p779-94, ISSN 0022-1007
Journal Code: I2V
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/46 (Item 13 from file: 155)
06778475 89080475
Restricted tissue distribution of Mlsa determinants. Stimulation of Mlsa-reactive T cells by B cells but not by dendritic cells or macrophages.
Webb SR; Okamoto A; Ron Y; Sprent J
Research Institute of Scripps Clinic, La Jolla, California 92037.
J Exp Med Jan 1 1989, 169 (1) p1-12, ISSN 0022-1007 Journal Code: I2V
Contract/Grant No.: CA-41993; CA-38355; CA-25803; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/47 (Item 14 from file: 155)
06691897 88336897
The SCID-hu mouse: murine model for the analysis of human hematolymphoid

Recine JH; Nishikawa K; Kaneshima H; Shultz LD; Lieberman M; Weissman IL
Department of Radiation Oncology, Stanford University School of Medicine, CA 94305.
Science Sep 23 1988, 241 (4873) p1632-9, ISSN 0036-8075
Journal Code: UJ7
Contract/Grant No.: CA03352; CA20408[illegible]/072
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/48 (Item 15 from file: 155)
06641077 88286077
Split tolerance induced by the intrathymic adoptive transfer of thymocyte stem cells.
Shimonkevitz RP; Bevan MJ
Department of Immunology, Research Institute of Scripps Clinic, La Jolla, California 92037.
J Exp Med Jul 1 1988, 168 (1) p143-56, ISSN 0022-1007
Journal Code: I2V
Contract/Grant No.: AI-07244; AI-19499; CA-25803
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/49 (Item 16 from file: 155)
06525847 88170847
Isolation of rat/rat T cell hybrids using W/Fu C58(NT)D as *fusion* partner.
Curling E; Slade C; Hutchinson I; Morris P
Nuffield Department of Surgery, University of Oxford, U.K.
J Immunol Methods Apr 6 1988, 108 (1-2) p171-8, ISSN 0022-1759
Journal Code: IFE
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/50 (Item 17 from file: 155)
06307662 87281662
Bi-specific monoclonal antibodies: selective binding and complement fixation to cells that express two different surface antigens.
Wong JT; Colvin RB
J Immunol Aug 15 1987, 139 (4) p1369-74, ISSN 0022-1767
Journal Code: IFB
Contract/Grant No.: R44-CA39965; T32-CA09216
Languages: ENGLISH
Document type: JOURNAL ARTICLE

12/3/51 (Item 18 from file: 155)
06286910 87260910
Expression of members of *immunoglobulin* gene family in somatic cell hybrids between human B and T cells.
Kozbor D; Burioni R; Ar-Rushdi A; Zmijewski C; Croce CM
Proc Natl Acad Sci U S A Jul 1987, 84 (14) p4969-73, ISSN 0027-8424
Journal Code: PV3
Contract/Grant No.: CA 39860
Languages: ENGLISH
Document type: JOURNAL ARTICLE
?ds

Set	Items	Description
S1	142	CD4 AND (IG OR IMMUNOGLOBIN OR IMMUNOGLOBULIN) AND (FUSION OR CHIMER?)
S2	101	RD (unique items)
S3	2	AU="BEAUDRY G"
S4	45	E3-E5
S5	47	S3 OR S4
S6	30	RD (unique items)
S7	2	S6 AND S1

S11 21 S9 AND PY=1992
S12 51 S9 NOT (S10 OR S11)
?t s11/3,ab/all

11/3,AB/1 (Item 1 from file: 157)
00077141 93096473 MED/93096473

Brain tumours and lymphomas in transgenic mice that carry HTLV-I LTR/c-myc and *Ig*/tax genes.

Benvenisty N; Ornitz DM; Bennett GL; Sahagan BG; Kuo A; Cardiff RD; Leder P

Department of Genetics, Harvard Medical School, Howard Hughes Medical Institute, Boston, Massachusetts 02115.

Oncogene Dec *1992*, 7 (12) p2399-405, ISSN 0950-9232
Journal Code: ONC

Languages: ENGLISH

Document Type: JOURNAL ARTICLE

The human T-cell leukemia virus type 1 (HTLV-I) is associated with adult *CD4* + T-cell leukemia (ATL) and tropical spastic paraparesis (TSP). In as much as only a small percentage of individuals infected with HTLV-I develop either disease, we set out to model a genetic partner for this virus in an effort to understand and possibly reproduce its pathophysiology. To this end we have developed a binary set of transgenic mice, one bearing the relatively inactive HTLV-I long terminal repeat (LTR) positioned to drive the c-myc oncogene and another bearing a *fusion* transgene consisting of the *immunoglobulin* promoter/enhancer driving the gene for the HTLV-I transcription activator, tax. Alone, the tax construct, though expressed in the thymus, spleen, lung and brain, has no deleterious effect. Alone, the HTLV-I LTR/c-myc construct is expressed at very low levels in lymphoid cells and occasionally induces lymphomas in older animals. When these two transgenic lines are mated, bigenic offspring harboring both transgenes exhibit dramatic tumor formation. As in the human, these animals develop *CD4* + T-cell lymphomas, but they also develop central nervous system tumors by 25-90 days of age. The syndrome, which is 100% penetrant and lethal, provides an animal model for adult T-cell lymphoma and a source of cultured cells of neurogenic origin.

11/3,AB/2 (Item 2 from file: 157)
00071878 92400714 ICA8/92400714

CD4 -derived peptide and dextran sulfate block antibody binding to the peptides from principal neutralizing domain (PND) and carboxy-terminal region of gp120.

Tarasova S; Neshcheryakova D; Andreev S; Khaitov R

Institute of Immunology, Moscow, Russia.

Int Conf AIDS Jul 19-24 *1992*, 8 (2) pA7 (abstract no. PoA 2027),

Languages: ENGLISH

Document Type: MEETING ABSTRACT

OBJECTIVE: To study the mechanisms of antiviral activity of *CD4*-derived peptide 75-99 and compare with the mode of blocking action for sulfated polysaccharides; to determine whether the electrostatic interactions between these negatively charged agents and positively charged HIV envelope fragments take place using the set of peptides from all high positive charged density regions of gp120 and gp41. METHODS: The peptides with the large amount of positively charged amino acids ("+"aa) and the control ones from gp120 including PND, N- and C-terminal parts (107-131, 301-319 and 307-329 BRU-strain, 301-323 MN-strain, 423-450, 495-516), and from gp41 (584-612, 602-624, 828-835, 842-861) were used as solid phase antigens in ELISA. Peptide AZ-2, 75-99 region from V1 *CD4* -KIEDSDTYIC(Acm)EVEDQKEEVQLLVFG (CDR3-*Ig* like) and dextran sulfate (DS, 8 and 500 kDa) were used as inhibitory agents of antibody binding by ELISA using: 1) anti-peptide rabbit antibodies, 2) sera from infected persons with different post infection times and disease manifestations. To distinguish the role of Lys and Arg in the electrostatic interaction the blocking of Lys positive charge was made. RESULTS AND DISCUSSION: We showed AZ-2 to inhibit syncytium formation tively: 50%-inhibition at 0.8 x

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PND- and gp120 C-terminal peptides. DS-8 and 500 both completely blocked binding of human PND-reactive antibodies with the peptides from BRU and MN strains at the same concentrations (0.1 micrograms/ml0; with gp120 C-terminal peptide--at the concentrat[illegible]-4 micrograms/ml. The analogous parameter for AZ-2 with these peptides was 125-250 micrograms/ml. It is interesting, the character of inhibitory curves (slope angle of linear part) was the same for AZ-2 and DS. The model system based on the rabbit anti-peptide antibodies was not sensitive enough as compared with human sera. The chemical modification of lysine amino groups resulted in complete failure of blocking activity for both DS and AZ-2. Summing up our results and taking into account HIV env sequence alignments we may assume the Lys residues neighbouring to Arg, i.e. LysArg/ArgLys are of main importance for DS or AZ-2 binding to gp120. The direct contacts between positive charged gp120 parts and negatively charged CDR3 part of *CD4* during virus entry into cell are proposed.

11/3,AB/3 (Item 3 from file: 157)
00053828 93058998 MED/93058998
Chimeric CD7 monoclonal antibody therapy in rheumatoid arthritis.
Kirkham BW; Thien F; Pelton BK; Pitzalis C; Amlot P; Denman AM; Panayi GS
Rheumatology Unit, United Medical School, Guy's Hospital, London, UK.
J Rheumatol Sep *1992*, 19 (9) p1348-52, ISSN 0315-162X
Journal Code: JWX
Languages: ENGLISH
Document Type: JOURNAL ARTICLE
Murine monoclonal antibody (Mab) therapy in patients with rheumatoid arthritis (RA) produces an antimouse *immunoglobulin* response by the recipient. We studied a *chimeric* (human/mouse) CD7 Mab, in a dose ranging tolerability study in 10 patients with RA. Modest improvements in disease activity occurred with frequent acute adverse effects of malaise, fever and nausea. After treatment, peripheral blood T lymphocyte numbers fell by 50% and CD7 expression fell by 97% for less than 7 days. Our study demonstrates *chimeric* Mab function in vivo and illustrates the influence of antibody isotype and patient characteristics on adverse effects.

11/3,AB/4 (Item 4 from file: 157)
00053698 93053070 MED/93053070
CD4 immunoadhesins in anti-HIV therapy: new developments.
Chamow SM; Duliege AM; Ammann A; Kahn JO; Allen JD; Eichberg JW; Byrn RA; Capon DJ; Ward RH; Ashkenazi A
Genentech, Inc., South San Francisco, CA 94080.
Int J Cancer Suppl *1992*, 7 p69-72, ISSN 0020-7136 Journal Code: GRM
Languages: ENGLISH
Document Type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
CD4 , the cell-surface receptor for the human immunodeficiency virus (HIV), is a member of the *immunoglobulin* (*Ig*) gene superfamily. It contains 4 extracellular sequences homologous to *Ig* variable domains, the first of which (V1) is sufficient for binding to HIV. To develop *CD4* as an anti-HIV therapeutic, we engineered a *CD4* immunoadhesin (*CD4*-IgG)--a *fusion* protein containing the V1 and V2 domains of *CD4* with the hinge and Fc regions of human *Ig* heavy chain. A *chimeric* protein of this type has several advantages compared to the soluble receptor, including a greatly extended in vivo half-life and greater avidity for HIV; moreover, like an antibody, it performs effector functions via its Fc domains, such as complement activation and antibody-dependent cell-mediated cytotoxicity. In vivo experiments show that *CD4* -IgG protects against HIV-1 IIIB infection of chimpanzees when administered prior to viral challenge. In addition, *CD4* -IgG is transferred efficiently across the placenta from mother to fetus in rhesus monkeys. To evaluate its safety in humans, we conducted a phase-I clinical trial in adult patients with AIDS and AIDS-related complex. We found that, in a total of 16 patients, administration of *CD4* -IgG was well tolerated at doses up to 1000 micrograms/kg of body weight, with no important clinical or immunological

CD4 -IgG to cross the placenta, we plan to focus future clinical efforts on preventing infection of newborns via maternal-fetal transfer of HIV.

11/3,AB/5 (Item 5 from file: 157)
00052783 93016879 MED/93016879
Characterization of the cDNA of a broadly reactive neutralizing human anti-gp120 monoclonal antibody.
Marasco WA; Bagley J; Zani C; Posner M; Cavacini L; Haseltine WA; Sodroski J
Division of Human Retrovirology, Dana Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115.
J Clin Invest Oct *1992*, 90 (4) p1467-78, ISSN 0021-9738
Journal Code: HS7
Contract/Grant No.: K08-CA01507, CA, NCI; AI31783, AI, NIAID
Languages: ENGLISH
Document Type: JOURNAL ARTICLE
The F105 mAb, identified in an HIV-1-infected individual, binds to a discontinuous epitope on the HIV-1 gp120 envelope glycoprotein, blocks the binding of gp120 to the *CD4* viral receptor, and neutralizes a broad range of HIV-1 isolates. This study reports the primary nucleotide and deduced amino acid sequences of the rearranged heavy and light chains of the mAb F105. This IgG1k mAb uses a VH gene member of the VH4 gene family (V71-4) and is productively rearranged with a D-D *fusion* product of the dlr4 and da4 germline DH genes and the JH5 gene. This rearranged heavy chain gene expresses the VH4-HV2a idiotope, which is seen in human monoclonal IgM cold agglutinins. The F105 Vk appears to be derived from the Humvk325 germline gene and is rearranged with a Jk2 gene. For both chains, the mutational pattern in the rearranged VH and VL genes is indicative of an antigen-driven process. These studies show that production of a broadly neutralizing anti-HIV-1 antibody that recognizes determinants within the *CD4* recognition site of the envelope glycoprotein is achieved by rearrangement of the V71-4 and Humvk325 germline variable region genes along with selected individual point mutations in the rearranged genes.

11/3,AB/6 (Item 6 from file: 157)
00050028 92373029 MED/92373029
Effects of *CD4* synthetic peptides on HIV type 1 envelope glycoprotein function.
Repke H; Gabuzda D; Palu G; Emmrich F; Sodroski J
Dana-Farber Cancer Institute, Department of Pathology, Harvard Medical School, Boston, MA 02115.
J Immunol Sep 1 *1992*, 149 (5) p1809-16, ISSN 0022-1767
Journal Code: IFB
Contract/Grant No.: P30 CA 06516, CA, NCI; P30 AI 28691, AI, NIAID; AI 24755, AI, NIAID; +
Languages: ENGLISH
Document Type: JOURNAL ARTICLE
Benzylated derivatives of a peptide (*CD4* (81-92)) representing the CDR3-like region of *CD4* were previously found to inhibit gp120 binding, HIV-1 infectivity, and syncytium formation. These results have been interpreted to indicate a role for the corresponding *CD4* region in these processes. The peptide (TbYICbEbVEDUKAcEE) is the prototype of a series of similar *CD4* (81-92) derivatives. We report that this peptide noncompetitively inhibits binding to *CD4* of both gp120 and a mAb (MAX.16H5), both of which recognize the CDR2-like region of *CD4*. The binding of an antibody (Leu 3a) that is directed against a different area of the D1 domain of *CD4* was also inhibited. The peptide derivative inhibited both HIV-1- and HTLV-1-mediated syncytium formation in the same concentration range. Nonbenzylated cyclic and linear peptides representing the CDR3-like region of *CD4* (*CD4*(84-101)) had only minor effects on gp120 binding which were not sequence specific. The results of this study suggest that the effects of benzylated *CD4*(81-92) derivatives on HIV-1 binding or *fusion* should not be used to reach conclusions about the function of the corresponding *CD4* reg-

00047270 92260823 MED/92260823

Human immunodeficiency virus type 2 infection and *fusion* of *CD4* -negative human cell lines: induction and enhancement by soluble *CD4*.

Clapham PR; McKnight A; Weiss RA

Chester Beatty Laboratories, Inst[illegible] of Cancer Research, London, England.

J Virol Jun *1992*, 66 (6) p3531-7, ISSN 0022-538X Journal Code: KCV

Languages: ENGLISH

Document Type: JOURNAL ARTICLE

We describe human immunodeficiency type 2 (HIV-2) strains which induce cell-to-cell *fusion* and infect certain *CD4*- human cell lines. Soluble *CD4* (sCD4) induces or enhances *fusion* by most HIV-2 strains tested. Soluble *CD4*-*immunoglobulin* G *chimeras* and conjugates of sCD4 and antibody to the third domain of *CD4* block HIV-2 *fusion* of *CD4*- cells. We conclude that HIV-2 can enter *CD4*- cells via an alternative cell surface receptor to *CD4*. While some strains entered efficiently, others retained a dependency on an interaction with sCD4 to initiate changes in the virion envelope required for membrane *fusion*.

11/3,AB/8 (Item 8 from file: 157)

00043069 92085388 MED/92085388

Virions of primary human immunodeficiency virus type 1 isolates resistant to soluble *CD4* (sCD4) neutralization differ in sCD4 binding and glycoprotein gp120 retention from sCD4-sensitive isolates.

Moore JP; McKeating JA; Huang YX; Ashkenazi A; Ho DD

Chester Beatty Laboratories, Institute of Cancer Research, London, United Kingdom.

J Virol Jan *1992*, 66 (1) p235-43, ISSN 0022-538X Journal Code: KCV

Contract/Grant No.: AI 25541, AI, NIAID; AI 26747, AI, NIAID; AI 27742, AI, NIAID; +

Languages: ENGLISH

Document Type: JOURNAL ARTICLE

Primary isolates of human immunodeficiency virus type 1 (HIV-1) are much less sensitive to neutralization by soluble *CD4* (sCD4) and sCD4-*immunoglobulin* (*Ig*) *chimeras* (*CD4* -IgG) than are HIV-1 strains adapted to growth in cell culture. We demonstrated that there are significant reductions (10- to 30-fold) in the binding of sCD4 and *CD4* -IgG to intact virions of five primary isolates compared with sCD4-sensitive, cell culture-adapted isolates RF and IIIB. However, soluble envelope glycoproteins (gp120) derived from the primary isolate virions, directly by detergent solubilization or indirectly by recombinant DNA technology, differed in affinity from RF and IIIB gp120 by only one- to threefold. The reduced binding of sCD4 to these primary isolate virions must therefore be a consequence of the tertiary or quaternary structure of the envelope glycoproteins in their native, oligomeric form on the viral surface. In addition, the rate and extent of sCD4-induced gp120 shedding from these primary isolates was lower than that from RF. We suggest that reduced sCD4 binding and increased gp120 retention together account for the relative resistance of these primary isolates to neutralization by sCD4 and *CD4* -IgG and that virions of different HIV-1 isolates vary both in the mechanism of sCD4 binding and in subsequent conformational changes in their envelope glycoproteins.

11/3,AB/9 (Item 1 from file: 155)

00561373 93271373

Failure of blood mononuclear cells from human donors with autoimmune haemolytic anaemia to reconstitute severe combined immunodeficient mice.

Macht LM; Leader KA; Corrall RJ; Yates P; Elson CJ

Department of Pathology and Microbiology, Medical School, Bristol.

Autoimmunity (SWITZERLAND) *1992*, 14 (2) p127-35, ISSN 0891-6934 Journal Code: A5H

Languages: ENGLISH

Document type: JOURNAL ARTICLE

autoimmune haemolytic anaemia (AIHA) was assessed. Upon transfer to SCID mice, PBMC from normal donors and patients with autoimmune thyroid disease (AITD) produced substantial levels of *immunoglobulin* (*Ig*), detectable in the plasma of recipient SCID mice. In contrast, the majority of PBMC from AIHA donors did not produce *Ig* in recipient mice. The capacity of PBMC to reconstitute SCID mice was not related to the donor's age. In one case, remission of AIHA allowed the donor's PBMC to successfully reconstitute SCID mice, despite the fact that the donor had developed immune thrombocytopenic purpura (ITP). AIHA PBMC were viable by dye exclusion and contained cells in various states of activation, as judged by their IgG secretion profiles when cultured in vitro. The proportions of leukocytes in AIHA PBMC (T to B cell ratios, *CD4*+ to CD8+ cell ratios and monocytes) were highly variable compared to non-AIHA PBMC. To determine the effect of abnormal lymphocyte proportions on SCID reconstitution, depletion experiments were carried out on normal and AITD PBMC. This work demonstrated a requirement for high T cell numbers, especially *CD4*+ cells, and minimal B cell numbers for successful reconstitution. CD8+ depletion of PBMC led to increased levels of *Ig* production in some instances. It is considered that PBMC from AIHA patients have a defect different from that of other autoimmune disorders, which renders them incapable of reconstituting SCID mice.

11/3,AB/10 (Item 2 from file: 155)
08410480 93120480

High-level expression and characterization of a mouse-human *chimeric* *CD4* antibody with therapeutic potential.

Looney JE; Knight DM; Arevalo-Moore A; Trinh H; Pak KY; Dalesandro MK; Rieber EP; Riethmuller G; Daddona PE; Ghrayeb J

Department of Molecular Biology, Centocor, Inc., Malvern, PA 19355.

Hum Antibodies Hybridomas (UNITED STATES) Oct *1992*, 3 (4) p191-200, ISSN 0956-960X Journal Code: A6A

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The use of murine anti-*CD4* monoclonal antibodies (MAbs) has shown considerable promise for the treatment of allograft rejection and rheumatoid arthritis. We have constructed mouse-human anti-*CD4* antibodies with the goal of increasing their clinical potential by decreasing immunogenicity and improving effector functions. The *chimeric* antibodies were constructed by cloning the heavy and light chain variable regions of M-T412, a murine antibody raised against the human *CD4* antigen, and joining them to the human G1, G4, or kappa constant regions in mammalian expression vectors. After transfection into mouse myeloma cells, stable cell lines were isolated that secrete up to 140 micrograms/ml *chimeric* antibody in static culture. The *chimeric* antibodies were equivalent to the murine antibody in their binding characteristics and relative affinities. However, the *chimeric* M-T412 MAbs have enhanced activity when compared to the murine G2a MAb in mediating antibody-dependent cell-mediated cytotoxicity using human *CD4*+ target and effector cells.

11/3,AB/11 (Item 3 from file: 155)
08356238 93066238

T-cell activation molecule 4-1BB binds to extracellular matrix proteins.

Chalupny NJ; Peach R; Hollenbaugh D; Ledbetter JA; Farr AG; Aruffo A

Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA 98121.

Proc Natl Acad Sci U S A (UNITED STATES) Nov 1 *1992*, 89 (21) p10360-4, ISSN 0027-8424 Journal Code: PV3

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The recently isolated 4-1BB cDNA clone encodes a cell surface protein expressed by activated T cells. Its extracellular domain is homologous to members of the nerve growth factor receptor super family and its cytoplasmic domain contains a sequence homologous to the binding site for the T-cell-specific tyrosine kinase p[illegible]und in the cytoplasmic domains

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was used in immunohistochemical studies to identify tissues that express the 4-1BB ligand. 4-1BB Kg bound to virtually all tissues examined, suggesting that extracellular components might function as its ligands. To explore this possibility, 4-1BB was expressed in COS cells and found to mediate the binding of fibronectin, vitronectin, laminin, and collagen VI but not of collagen I. The binding of extracellular matrix proteins to 4-1BB was not mediated by Arg-Gly-Asp (RGD) or CS-1 amino acid sequences. Experiments with overlapping proteolytic fragments of fibronectin showed that 4-1BB interacts with multiple regions of fibronectin. The interaction between extracellular matrix proteins and 4-1BB was completely blocked by the anionic carbohydrate polymer fucoidan and was partially blocked by the anionic carbohydrate polymer dextran sulfate and the glycosaminoglycan heparin sulfate but was unaffected by desulfated heparin. These results suggest that carbohydrates may play a role in mediating the 4-1BB-extracellular matrix protein adhesion.

11/3,AB/12 (Item 4 from file: 155)
08339623 93049623

Co-stimulation of murine *CD4* T cell growth: cooperation between B7 and heat-stable antigen.

Liu Y; Jones B; Brady W; Janeway CA Jr; Linley PS
Section of Immunobiology, Yale University School of Medicine, New Haven.
Eur J Immunol (GERMANY) Nov *1992*, 22 (11) p2855-9, ISSN 0014-2980
Journal Code: ENS
Contract/Grant No.: AI-26810, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The B cell activation antigen B7/BB1 has been shown to co-stimulate growth of human T cells by binding the T cell molecule CD28. In mice, the heat-stable antigen (HSA) has also been shown to act as a co-stimulator for T cell growth. In this study, we have evaluated the contributions of B7 and HSA to the co-stimulatory activity of antigen-presenting cells (APC). Mouse B7 provides co-stimulatory activity for murine *CD4* T cells in anti-CD3-induced proliferation. Human CTLA4Ig, a *chimeric* molecule comprising the extracellular region of CTLA-4 fused to an *immunoglobulin* C gamma fragment, binds to murine B7. We, therefore, use human CTLA4Ig and the hamster anti-HSA monoclonal antibody 20C9 to analyze the relative contributions of B7 and HSA to the co-stimulatory activity of murine spleen APC. Our data reveal that both murine B7 and HSA are expressed by dendritic cells and by low-density spleen B cells. Either CTLA4Ig alone or anti-HSA alone inhibited *CD4* T cell proliferation to anti-CD3 by > 90%, while CTLA4Ig and anti-HSA together were far more efficient in inhibiting clonal expansion of *CD4* T cells. These results demonstrate that functionally defined co-stimulation involves at least B7 and HSA and suggest that signals delivered by B7 and HSA synergize in promoting T cell growth.

11/3,AB/13 (Item 5 from file: 155)
08301452 93011452

Activated human T cells express a ligand for the human B cell-associated antigen CD40 which participates in T cell-dependent activation of B lymphocytes.

Lane P; Traunecker A; Hubele S; Inui S; Lanzavecchia A; Gray D
Basel Institute for Immunology, Switzerland.
Eur J Immunol Oct *1992*, 22 (10) p2573-8, ISSN 0014-2980
Journal Code: ENS
Languages: ENGLISH
Document type: JOURNAL ARTICLE

To identify the ligand for the B cell-associated antigen CD40, we constructed a *chimeric* *immunoglobulin* molecule where the extracellular portion of the CD40 protein replaced the normal *immunoglobulin* variable region. No binding was detected on resting peripheral blood T cells. However, following T cell activation with phorbol esters and ionomycin, the *chimeric* protein bound specifically to activated human T cells and precipitated a 35-kDa protein from such cells. The induction of the CD40

ligand was detectable on the cell surface after 1 h, with maximal expression after 8 h of stimulation. The T cells expressing CD40 ligand were predominantly *CD4* positive, although a proportion of CD8-positive cells also expressed the protein. There was no particular correlation with CD45 phenotype. Finally, we found that soluble CD40 inhibited T-dependent B cell proliferation. The results are discussed in the context of cognate interactions between B and T cells.

11/3,AB/14 (Item 6 from file: 155)
08299082 93009082

Human *immunoglobulin* production in immunodeficient mice: enhancement by immunosuppression of host and in vitro activation of human mononuclear cells.

Cavacini LA; Kennel M; Lally EV; Posner MR; Quinn A
Department of Immunobiology, Centocor, Inc., Malvern, PA.

Clin Exp Immunol Oct *1992*, 90 (1) p135-40, ISSN 0009-9104
Journal Code: DD7
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The affect of host and donor related factors on successful engraftment of human cells into mice was examined to minimize the variability that has been observed in successful development of human-mouse *chimera* for the study of human disease and immune physiology and regulation. Human *immunoglobulin* production in severe combined immunodeficiency (SCID) mice engrafted with human peripheral blood mononuclear cells (PBMC) was augmented by immunosuppressing recipient mice and activating donor PBMC. Immunosuppression of recipient mice with 3 Gy of gamma-irradiation induced a 10-fold increase in human IgG in the sera of engrafted SCID mice. Variation in production of human IgG in recipient mice correlated with preinjection phenotype and activation status of injected PBMC. Mice injected with PBMC with a low *CD4*/CD8 ratio (less than 0.5) produced no detectable circulating human *immunoglobulin*. When the *CD4*/CD8 ratio was greater than 1.5, human IgG was detected in sera of PBMC-recipient SCID mice. Serum IgG increased 10-fold following in vitro activation of donor PBMC with anti-CD3, IL-2 and Staphylococcus aureus. Successful engraftment and serum IgG production was evidenced by an increase in the recovery of activated human IgG+ cells in the spleens of mice with maximal IgG production. Optimization of functional engraftment required modification of both the host (SCID mice) and the donor cells.

11/3,AB/15 (Item 7 from file: 155)
08270005 92400005

Phenotypes of murine leukemia virus-induced tumors: influence of 3' viral coding sequences.

Ott DE; Keller J; Sill K; Rein A
Laboratory of Molecular Virology and Carcinogenesis, ABL-Basic Research Program, PRI/DynCorp, Inc., Frederick, Maryland.

J Virol Oct *1992*, 66 (10) p6107-16, ISSN 0022-538X Journal Code: KCV
Contract/Grant No.: N01-CO-74101, CO, NCI; N01-CO-74102, CO, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Murine leukemia viruses (MuLVs) induce leukemias and lymphomas in mice. We have used fluorescence-activated cell sorter analysis to determine the hematopoietic phenotypes of tumor cells induced by a number of MuLVs. Tumor cells induced by ecotropic Moloney, amphotropic 4070A, and 10A1 MuLVs and by two *chimeric* MuLVs, Mo(4070A) and Mo(10A1), were examined with antibodies to 13 lineage-specific cell surface markers found on myeloid cell, T-cell, and B-cell lineages. The *chimeric* Mo(4070A) and Mo(10A1) MuLVs, consisting of Moloney MuLV with the carboxy half of the Pol region and nearly all of the Env region of 4070A and 10A1, respectively, were constructed to examine the possible influence of these sequences on Moloney MuLV-induced tumor cell phenotypes. In some instances, these phenotypic analyses were supplemented by Southern blot analysis for lymphoid

heavy-chain, the T-cell receptor gamm[illegible] the T-cell receptor beta loci. The results of our analysis showed that M[illegible]ney MuLV, 4070A, Mo(4070A), and Mo(10A1) induced mostly T-cell tumors. Moloney MuLV and Mo(4070A) induced a wide variety of T-cell phenotypes, ranging from immature to mature phenotypes, while 4070A induced mostly prothymocyte and double-negative (*CD4* - CD8-) T-cell tumors. The tum[illegible]notypes obtained with 10A1 and Mo(10A1) were each less variable tha[illegible]e obtained with the other MuLVs tested. 10A1 uniformly induced a tumor consisting of lineage marker-negative cells that lack lymphoid cell-specific DNA rearrangements and histologically appear to be early undifferentiated erythroid cell-like precursors. The Mo(10A1) *chimera* consistently induced an intermediate T-cell tumor. The *chimeric* constructions demonstrated that while 4070A 3' pol and env sequences apparently did not influence the observed tumor cell phenotypes, the 10A1 half of pol and env had a strong effect on the phenotypes induced by Mo(10A1) that resulted in a phenotypic consistency not seen with other viruses. This result implicates 10A1 env in an active role in the tumorigenic process.

11/3,AB/16 (Item 8 from file: 155)
08063850 92201850

Identification of the *immunoglobulin* binding regions (IBR) of Fc gamma RII and Fc epsilon RI.

Hogarth PM; Hulett MD; Ierino FL; Tate B; Powell MS; Brinkworth RI
Helen M. Schutt Laboratory for Immunology, Austin Research Institute, Austin Hospital, Heidelberg, Victoria, Australia.

Immunol Rev Feb *1992*, 125 p21-35, ISSN 0105-2896 Journal Code: GG4
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

11/3,AB/17 (Item 9 from file: 155)
08028373 92166373

Comparison of GK1.5 and *chimeric* rat/mouse GK1.5 anti-*CD4* antibodies for prolongation of skin allograft survival and suppression of alloantibody production in mice.

Rashid A; Auchincloss H Jr; Sharon J
Department of Pathology, Boston University School of Medicine, MA 02118.

J Immunol Mar 1 *1992*, 148 (5) p1382-8, ISSN 0022-1767
Journal Code: IFB
Contract/Grant No.: AI23909, AI, NIAID; HL36377, HL, NHLBI; HL18646, HL, NHLBI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

GK1.5 is a rat mAb that recognizes the mouse *CD4* Ag. It has been shown to deplete *CD4* + cells in vivo and to be immunosuppressive. To evaluate the effect of the C region of this antibody in achieving cell depletion, *chimeric* antibodies, each having the rat GK1.5 V regions and one of the four mouse IgG C region isotypes, were compared with the native rat antibody. The *chimeric* antibodies and the native antibody were tested for their ability to mediate in vitro C-dependent cytotoxicity, in vivo cell depletion, and prolongation of allogeneic skin graft survival and suppression of alloantibody production. In vitro C-dependent cytotoxicity assays revealed that rat IgG2b and the *chimeric* antibodies containing mouse IgG2a, mouse IgG2b, and mouse IgG3 were effective in lysing *CD4*+ lymphocytes whereas mouse IgG1 was ineffective. In vivo studies of *CD4*+ cell depletion showed that mouse IgG2a, rat IgG2b, and mouse IgG2b were effective isotypes, mouse IgG1 was less effective, and mouse IgG3 did not deplete *CD4* + cells. A correlation was found between the ability of an isotype to deplete *CD4* + cells in vivo and its ability to prolong the survival of skin allografts and to suppress alloantibody production. The nondepleting mouse IgG3 was ineffective in these assays. Overall the most effective mouse isotype was IgG2a which was as effective as rat IgG2b. These results indicate 1) that syngeneic isotypes of mAb can cause cell depletion and consequently the prolongation of allograft rejection and

11/3,AB/18 (Item 10 from file: 155)
08000953 92138953

Propagation of a mouse myeloma cell line J558L producing human *CD4* *immunoglobulin* G1.

Schlaeger EJ; Schumpp B

Pharma Research, New Technologies, F. Hoffmann-LaRoche Ltd., Basle, Switzerland.

J Immunol Methods Jan 21 *1992*, 146 (1) p111-20, ISSN 0022-1759 Journal Code: IFE

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Transfected mouse myeloma cells are of increasing interest for the production of a wide variety of solubilised recombinant *fusion* proteins. A stably transfected J558L mouse myeloma subclone (J558L-*CD4*) secreting human *CD4*-*immunoglobulin* type G1 receptor (*CD4* -H gamma 1) was employed as a model system for cell suspension culture and expression of chimaeric molecules. Cells were grown up to 3-5 x 10(6) cells/ml in serum-free and protein-reduced DHI medium consisting of a mixture of DMEM, HamF12 and IMDM media supplemented with transferrin, insulin, Primatone RL and Pluronic F68. Primatone RL was the essential growth-promoting factor in protein-free medium. The soluble *CD4*-H gamma 1 receptor, the production of which was not growth-associated, accumulated in the medium to concentrations of 40 micrograms/ml with a specific formation rate of 0.18 micrograms/10(6) cells/h in conventional cultures. The cell density was further increased by growing the cells in dialysis tubing or by using a perfusion system with cell retention. Because of the continuous exchange of nutrients and metabolic end-products average concentrations of 35 x 10(6) cells/ml were achieved. *CD4*-H gamma 1 accumulated in the dialysis tubing up to 1.3 mg/ml. After an initial rapid growth period, a ten-fold reduction in specific nutrient consumption rates and metabolic end-product formation was observed. Chimaeric proteins purified by protein G chromatography from conventional and perfusion cultures were indistinguishable when compared by SDS-PAGE, limited proteolysis and isoelectric focusing analysis (isoelectric point: 8.5-8.6).

11/3,AB/19 (Item 11 from file: 155)
07975243 92113243

Intercellular adhesion molecule-2, a second counter-receptor for CD11a/CD18 (leukocyte function-associated antigen-1), provides a costimulatory signal for T-cell receptor-initiated activation of human T cells.

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Languages: ENGLISH

Document type: JOURNAL ARTICLE

Activation of T cells often requires both activation signals delivered by ligation of the TCR and those resulting from costimulatory interactions between certain T cell surface accessory molecules and their respective counter-receptors on APC. CD11a/CD18 complex on T cells modulate the activation of T cells by interacting with its counter-receptors intracellular adhesion molecule (ICAM-1) (CD54) and/or ICAM-2 on the surface of APC. The costimulatory ability of ICAM-1 has been demonstrated. Using a soluble ICAM-2 *Ig* *fusion* protein (receptor globulin, Rg) we demonstrate the costimulatory effect of ICAM-2 during the activation of *CD4* + T cells. When coimmobilized with anti-TCR-1 mAb ICAM-2 Rg induced vigorous proliferative response of *CD4* + T cells. This costimulatory effect of ICAM-2 was dependent on its coimmobilization with mAb directed at the CD3/TCR complex but not those directed at CD2 or CD28. Both resting as well as Ag-primed *CD4*+ T cells responded to the costimulatory effects of ICAM-2. The addition of mAb directed CD11a or CD18 molecules almost completely inhibited the responses to ICAM-2 Rg. These results are

completely inhibited the responses to ICAM-2 Rg. These results are consistent with the role of CD11a/CD18 complex as a receptor for ICAM-2 mediating its costimulatory effects. Stimulation of T cells with coimmobilized anti-TCR-1 and ICAM-2 resulted in the induction of IL-2R (CD25), and anti-Tac (CD25) mAb inhibited this response suggesting the contribution of endogenously synthesized IL-2 during this stimulation. These results demonstrate that like its homologue ICAM-1, ICAM-2 also exerts a strong costimulatory effect during the TCR-initiated activation of T cells. The costimulatory effects generated by the CD11a/CD18:ICAM-2 interaction may be critical during the initiation of T cell activation by ICAM-1low APC.

11/3,AB/20 (Item 12 from file: 155)
07973617 92111617

CD4 binding to major histocompatibility complex class II antigens induces LFA-1-dependent and -independent homotypic adhesion of B lymphocytes.

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Journal Code: ENS

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Document type: JOURNAL ARTICLE

T helper cells recognize processed antigen (Ag) in the context of major histocompatibility complex (MHC) class II antigens present on the surface of B cells and other Ag-presenting cells. This interaction is mediated through the T cell receptor complex with associate recognition of class II molecules by the *CD4* molecule. In this study, the binding of a soluble recombinant *CD4*/*Ig* heavy chain *fusion* protein (*CD4*-gamma 3) or monoclonal antibody (mAb) to class II antigens on human B cells was shown to induce rapid and specific homotypic adhesion of B cells and most B lymphoblastoid cell lines. mAb reactive with *CD4* inhibited *CD4*-gamma 3-induced adhesion and a mutant B lymphoblastoid cell line deficient in class II antigens failed to respond. Induction of homotypic adhesion was dependent on energy metabolism and a functional cytoskeleton, and class II+ pre-B cells did not exhibit adhesion in response to these stimuli, suggesting that cross-linking of class II molecules generated a transmembrane signal and did not simply aggregate cells. In addition, MHC class II-induced adhesion was Fc receptor independent, as 15 mAb of different *Ig* isotypes reactive with HLA-D or HLA-DR gene products induced adhesion. Anti-class II mAb and *CD4*-gamma 3 were able to induce adhesion at concentrations as low as 10 ng/ml and 100 ng/ml, respectively. Suboptimal stimulation of B cell lines through HLA-D antigens induced homotypic adhesion that was dependent on the activation of LFA-1 (CD11a/CD18), and which could be blocked by specific mAb. However, at greater signal strengths, adhesion was not blocked by mAb against the known adhesion receptors, suggesting the induction of a novel adhesion pathway. Consistent with this, homotypic adhesion induced by engagement of MHC class II antigens was observed with LFA-1-deficient B cell lines, and was independent of CD49d or CD18 expression. Thus, the direct engagement of B cell class II antigens by *CD4* is likely to generate transmembrane signals which trigger both LFA-1-dependent and LFA-1-independent adhesion pathways.

11/3,AB/21 (Item 13 from file: 155)
07953784 92091784

Expression of a functional *chimeric* *Ig*-MHC class II protein.

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Journal Code: IFB

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regions derived from anti-human *CD4* mAb MT310. Expression vectors were constructed containing the functional, rearranged gene segments coding for the V region domains of the antibody H and L chains in place of the first domains of the complete structural genes of the I-E alpha- and beta-chains, respectively. Cells transfected with both hybrid genes expressed a stable protein product on the cell surface. The *chimeric* molecule exhibited the idiotype of the antibody MT310 as shown by binding to the anti-idiotypic mAb 20-46. A protein of the anticipated molecular mass was immunoprecipitated with anti-mouse IgG antiserum. Furthermore, human soluble *CD4* did bind to the transfected cell line, demonstrating that the *chimeric* protein possessed the binding capacity of the original mAb. Thus, the hybrid molecule retained: 1) the properties of a MHC class II protein with regard to correct chain assembly and transport to the cell surface; as well as 2) the Ag binding capacity of the antibody genes used. The generation of hybrid MHC class II molecules with highly specific, non-MHC-restricted binding capacities will be useful for studying MHC class II-mediated effector functions such as selection of the T cell repertoire in thymus of transgenic mice.
?ds

Set	Items	Description
S1	142	CD4 AND (IG OR IMMUNOGLOBIN OR IMMUNOGLOBULIN) AND (FUSION OR CHIMER?)
S2	101	RD (unique items)
S3	2	AU="BEAUDRY G"
S4	45	E3-E5
S5	47	S3 OR S4
S6	30	RD (unique items)
S7	2	S6 AND S1
S8	2	S6 AND S2
S9	99	S2 NOT S8
S10	27	S9 AND PY=1993
S11	21	S9 AND PY=1992
S12	51	S9 NOT (S10 OR S11)

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$1.22 Estimated cost FilePause
$1.12 0.034 Hrs File157
$3.96 33 Type(s) in Format 3
$1.68 14 Type(s) in Format 4 (UDF)
$5.64 47 Types
$6.76 Estimated cost File157
$7.26 0.220 Hrs File155
$2.16 18 Type(s) in Format 3
$0.12 1 Type(s) in Format 3 (UDF)
$1.44 12 Type(s) in Format 4 (UDF)
$3.72 31 Types
$10.98 Estimated cost File155
OneSearch, 2 files, 0.283 Hrs FileOS
$3.40 DIALNET
$22.36 Estimated cost this search
$22.50 Estimated total session cost 0.288 Hrs.
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